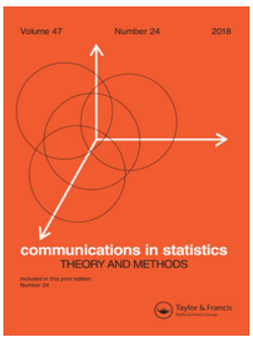

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Statistical Methods for Individual-Level Data in Cohort Mortality Studies of Rheumatic Diseases

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In the field of rheumatic diseases, prospective individual-level data on (prevalent) cohorts of patients over a long period of time are collected. One of the many uses of such data is to investigate mortality. Excess mortality, time trends (temporal variation) in mortality rates, life expectancy and life years lost of patients, and risk factors for mortality may all be of interest. In this article, we show how careful application of Poisson and Cox relative risk regression models can be used to tackle these questions, illustrating the methods with cohort data from patients with systemic lupus erythematosus and psoriatic arthritis. For external comparisons of a cohort with a standard (or reference) population, Poisson regression can be used to generalize the usual standardized mortality ratio (SMR) analyses. For assessing the pattern of (excess) mortality over time, unadjusted and adjusted "rolling average" SMRs are developed and shown to provide further insight concerning an observed decline in SMR over time for psoriatic arthritis patients. An extension of the traditional life expectancy and years of life lost calculations is also derived. For comparisons within a cohort, we demonstrate how Cox regression models can incorporate time measured on a variety of scales to allow the identification of a calendar time decline in mortality risk for lupus patients which is demonstrably independent of possible declines with disease duration and/or time in clinic and of other disease related explanatory variables.

Keywords Cox regression; Life expectancy; Life table; Person-years; Poisson regression; Psoriatic arthritis (PsA); Standardized mortality ratio (SMR); Systemic lupus erythematosus (SLE); Time trend; Years of life lost.

Mathematics Subject Classification Primary 62N99; Secondary 92C60.

1. Introduction

In rheumatic diseases, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), and systemic lupus erythematosus (SLE), patient cohorts, which incorporate routine prospective collection of individual-level data, are of particular value. They may be

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used for various research purposes including characterization of disease progression, exposures associated with death or comorbidites such as cancer or heart disease, and comparative studies of health related events in patient and general populations. Temporal trends may be of particular interest.

While such long-term individual-level data are of considerable value, there are complications to the use of such data. Over a long time period, the mix of patients seen may vary. In addition, there will be changes in the pattern of standard care due to the adoption of new treatment strategies. Many other factors, within patient populations and reflecting societal health trends more generally, will also demonstrate time varying behaviour. Here, we focus particularly on mortality studies although much of the methodology will be more generally applicable. In summarizing and assessing the mortality experience of a patient cohort over time, these issues associated with long-term longitudinal data need consideration when choosing appropriate statistical methodology. Of particular concern will be the choice and handling of time scale(s). The time at which any data are collected can be specified in terms of calendar time (day/month/year), the age of the patient, and the time over which the patient has had the disease, usually referred to as disease duration. The links between these time scales lead to non identifiability issues. More generally, any analysis strategy will need to reflect the variation in mortality rates due to a variety of explanatory variables, including generic factors such as age, sex, and calendar period but also disease specific variables.

In subsequent sections, we outline statistical and epidemiological methods for analysing individual-level data from prevalent cohorts of rheumatic patients when death (all cause mortality) is the outcome of interest. In Sec. 2, we give a brief introduction to psoriatic arthritis and systemic lupus erythematosus and to the two cohorts, followed at the University of Toronto's Psoriatic Arthritis and Lupus Clinics, used to illustrate our methods. Needed notation and a general model framework are provided in Sec. 3. A particular emphasis is on establishing a notation which captures the various time scales of relevance.

Section 4 considers methods to make an external comparison of the mortality experience of a patient cohort with that of the general population. The focus is on the standardized mortality ratio (SMR), the ratio of the observed number of deaths in a study cohort to the expected number of deaths that would occur if the age-sex-calendar period specific death rates of an appropriate reference population were those of the cohort. This is the classical way of measuring, through an indirect method of adjustment, the excess mortality in a cohort. With long-term patient data however, a single SMR, even though its calculation is appropriately comparative and "dynamic", can be a simplistic summary of the information in the data. Therefore, we develop generalized methods which provide "rolling average" and explanatory variable adjusted SMRs. These are used to assess whether there is an improvement in (excess) mortality over calendar period. These generalizations are implemented via Poisson regression. In addition, an extension of the traditional calculation of life expectancy and life years lost to take account of the calendar-period variation in (annual) life-table mortality rates is proposed.

Section 5 presents methods for comparisons within a cohort. For such internally controlled analyses, relative risk regression models (Cox, 1972) are suggested as appropriate. This methodology, which we refer to subsequently as Cox regression models, easily accounts for left truncation (delayed entry) and we demonstrate further how it can be used to aviod the non identifiability features of age-period-cohort models. In the application considered, calendar period effects are

of particular interest, while age is the primary time-scale for mortality risk, and adjustment for entry cohort effects and other disease-related explanatory variables is required. A comprehensive discussion of alternative methodology is beyond the scope of this article and therefore age-period-cohort Poisson models (Holford, 2005) are only discussed implicitly and relative survival (Dickman et al., 2004) is not discussed. Brief concluding remarks are given in Sec. 6.

2. Two Rheumatological Cohorts

Psoriatic arthritis is a chronic inflammatory arthritis associated with psoriasis. It is usually seronegative for rheumatoid factor, which distinguishes it from rheumatoid arthritis. The disease affects men and women almost equally, with a mean age of onset of 36 years (Gladman, 2004). It is characterized by bony proliferation and ostelysis, particularly at tendon, ligament and capsular insertions (entheses). In the past, it was thought to be a benign arthropathy. However recent investigations have suggested that PsA is more serious than previously thought. In the PsA cohort we consider, patients received follow-up care (roughly at 6–12-month intervals) according to a standard protocol at the University of Toronto PsA Clinic between 1978 and 2004. There were 680 patients enrolled during this period. Of these, 385 (56.6%) were men and 295 (43.4%) were women. Information on patient deaths was collected prospectively. During this 26-year period, 106 deaths were reported, 51 in men and 55 in women. The most common known causes of death were cancer and cardiovascular disease (Ali et al., 2007).

Systemic lupus erythematosus (SLE) is a chronic multisystem disorder of presumed autoimmune origin in which cytotoxic antibodies, or circulating immune complexes, give rise to tissue damage often resulting in damage to organ systems, such as the renal, skin, pulmonary, cardiovascular, musculoskeletal, peripheral vascular and nervous, as well as associated mortality (Urowitz and Gladman, 2000). It is characterised by fluctuating disease activity, with periods of illness alternating with periods of remission. Lupus occurs predominantly in females and at any age with most patients developing it between the ages of 15 and 45.

During the period of 1970–2005, 1,241 patients (1,083 females and 158 males) were enrolled into the University of Toronto Lupus Clinic. Patients were followed-up using a standardized protocol every 2–6 months regardless of disease activity or severity and were supervised by the same group of researchers over the entire period. In this cohort, the major approaches to therapy have been oral corticosteroids, antimalarials, and the antimetabolites azathioprine and methotrexate, with mycophenylate not being introduced until after 2005. There were 211 deaths over this 36-year period, 171 females and 40 males.

3. Notation and Model Framework

In a cohort mortality study, individuals are followed up from entry into the cohort until death or a censored follow-up time. For rheumatological patient cohorts, additional individual-level data is typically recorded at specific time points, usually clinic visits, within this interval. Time of entry often does not coincide with time of diagnosis as patients may be selected for (perhaps through referral to a clinic) the cohort sometime after diagnosis. For a mortality study, patients are assumed "at risk" from entry to the cohort to either the date of death or either the date of

analysis or the date lost to follow-up (depending on censoring assumptions made), whichever of the dates is the earlier.

Formally, let $(A_1^*, P_1^*), \ldots, (A_N^*, P_N^*)$ denote the (time to death from birth (i.e., age at death), calendar time of death) pairs of the N patients in the cohort, and assume that they are independently distributed random vectors each with density $f_i(a, p)$, survivor function $S_i(a, p)$ and hazard (death intensity) function $\lambda_i(a, p)$ for $i = 1, \ldots, N$. Let $(C_1, R_1), \ldots, (C_N, R_N)$ be the right-censoring ages and calendar times associated with the (A_i^*, P_i^*)'s, which are assumed to be uninformative. Further, let $(E_1, Q_1), \ldots, (E_N, Q_N)$ denote the (age at entry to the cohort, calendar time of entry) pairs for the N patients. We assume for the ith individual that the "left truncation" (age at entry, entry calendar time) random vector (E_i, Q_i) and the follow-up time to death from entry U_i^* are conditionally independent given the explanatory variable information $Z_i(\cdot)$.

At the time of analysis, we are in a position to observe the triplets

$$(A_1, P_1, \delta_1), \ldots, (A_N, P_N, \delta_N),$$

where

$$A_i = \min(A_i^*, C_i),$$
$$P_i = \min(P_i^*, R_i)$$

and

$$\delta_i = I(A_i^* \le C_i) = \begin{cases} 1 & \text{if } A_i^* \le C_i, \text{ that is, } A_i^* \text{ is not censored} \\ 0 & \text{if } A_i^* > C_i, \text{ that is, } A_i^* \text{ is censored.} \end{cases}$$

That is, we know either the ages and calendar times at death of those individuals who have died within the study period or the ages and calendar times at the times of censoring (which is either at analysis time or time of lost to follow-up) for those who are not known to have died within the study period. In addition, we define the random variable corresponding to the follow-up time in the study for the ith patient to be U_i, where $U_i = A_i - E_i = P_i - Q_i$. Estimation can be based on the likelihood, $l(\phi)$, given by

$$\begin{aligned} l(\phi) &= \prod_{i=1}^{N} \left(\frac{f_i(a_i, p_i; \phi)}{S_i(e_i, q_i; \phi)} \right)^{d_i} \left(\frac{S_i(a_i, p_i; \phi)}{S_i(e_i, q_i; \phi)} \right)^{1-d_i} \\ &= \prod_{i=1}^{N} \lambda_i(a_i(u_i), p_i(u_i))^{d_i} \exp\left[- \int_0^{u_i} \lambda_i(e_i + v, q_i + v) dv \right], \end{aligned}$$

where $a_i \equiv a_i(u_i)$, $p_i \equiv p_i(u_i)$, d_i is the realized value for δ_i, the integral is over those parts of the individuals' Lexis unit-slope life-line trajectories that are contained within their follow-up intervals, left truncation is accommodated and ϕ corresponds to the vector of parameters up to which the probability distribution is specified. The corresponding log-likelihood, $L(\phi)$, is

$$L(\phi) = \sum_{i=1}^{N} \left[d_i \log \lambda_i(a_i(u_i), p_i(u_i)) - \int_0^{u_i} \lambda_i(e_i + v, q_i + v) dv \right]. \tag{1}$$

The effects of explanatory variables are sensibly modelled through the hazard function and here we adopt a multiplicative intensity model

$$\lambda_i(a(u), p(u)) = \lambda_0(a, p) \exp(\beta^T z_i(u)), \tag{2}$$

where $\lambda_0(.,.)$ corresponds to the baseline hazard, and any non-negative functional of the linear predictor $\beta^T z$ could be used but where the exponential function is taken for convenience.

Whether $\lambda_0(.,.)$ is assumed known, known up to unknown parameters, or completely unknown leads to models already proposed in the literature and described in later sections. Here we use the connection between Poisson regression models for count data and the analysis of survival time data, when time is partitioned into intervals within which Poisson processes approximate the survival process. This connection has been known, at least, since Aitkin and Clayton (1980), and subsequently has been noted and discussed by many authors (Berry, 1983; Breslow et al., 1983; Frome, 1983; Holford, 1980; Laird and Olivier, 1981; Whitehead, 1980; Whittemore, 1985).

More specifically, the follow-up (observation) period for the cohort can be split into disjoint time-bins (partitions of the (age, time)-plane into bins whose union contains the observation period), where the intensity (hazard) for each individual in a bin is constant given the history (i.e., a piecewise constant (exponential) intensity), but is allowed to vary between bins. That is, in (2), the baseline hazard is assumed the same across individuals within each bin and the explanatory variables of an individual are assumed to remain constant within a bin. Denoting a bin by (s, t), corresponding to an age-band s and calendar period t, one can then show that the log-likelihood (1) may be written as

$$L(\phi) = \sum_{i=1}^{N} \sum_{s=0}^{S} \sum_{t=0}^{T} d_{ist} \log \lambda_{0st} \exp(\beta^T z_{ist}) - \sum_{i=1}^{N} \sum_{s=0}^{S} \sum_{t=0}^{T} \lambda_{0st} \exp(\beta^T z_{ist}) y_{ist}, \tag{3}$$

where λ_{0st} represents the constant baseline hazard rate in the (s, t)th time-bin, z_{ist} is the constant (or locally time-independent) explanatory variable vector for the ith patient within the (s, t)th time-bin, d_{ist} is an indicator variable, indicating whether the ith patient survives ($d_{ist} = 0$) or dies ($d_{ist} = 1$) in the (s, t)th time-bin, and y_{ist} is the time observed at risk within the (s, t)th time-bin for the ith patient along his/her unit life-line. In addition, the (s, t) time-bins can be further stratified by factors such as sex and race.

Then (3) is just the kernel of the log-likelihood for independent Poisson random variables $\{d_{ik}\}$ with means $\{\lambda_{0k} \exp(\beta^T z_{ik}) y_{ik}\}$, where $k \equiv k(s, t)$ indexes the (s, t) bins (possibly further stratified). Therefore, software for Poisson regression may be used to fit this model and to make inferences.

4. External Comparisons

4.1. *Standardized Mortality Ratio*

The standardized mortality ratio (SMR) is an indirect standardization measure which uses known reference rates stratified by time (e.g., age and calendar time period) and other factors (sex, race, etc.). It gives a measure of the possible excess mortality in the cohort compared to that in a standard population. The reference rates are

usually obtained from standard actuarial age-specific life-table estimated national mortality rates, possibly stratified by sex and race. These calendar period-dependent age-specific "life tables" will be referred to as dynamic "life-tables", as the reference age-specific mortality rates vary over calendar period.

The standard formula for calculating the overall SMR is

$$\text{SMR} = \frac{\sum_{i=1}^{N} d_i}{\sum_{k=1}^{K} \lambda_k^* y_k} = \frac{D}{E}, \tag{4}$$

where k corresponds to stratum, $D = \sum_{i=1}^{N} d_i$ is the total observed deaths in the cohort, λ_k^* is the reference population rate in stratum k, y_k is the cohort's total time at risk (generally person-years at risk) in stratum k, and E is the total deaths expected in the cohort based on the reference rates.

The overall SMR can be equivalently obtained by assuming that the stratum-specific cohort mortality rates are a constant multiple θ of the corresponding known stratum-specific reference rates. That is, $\lambda_{ik(s,t)} = \lambda^*_{k(s,t)}\theta$ for all k, where $\theta = \exp(\beta_0)$. Then, if we assume, for $i = 1, \ldots, N$, that $d_{ik(s,t)} \overset{indep}{\sim} Po(\lambda_{ik(s,t)} y_{ik(s,t)})$ and that $\log \lambda_{ik(s,t)} = \beta_0 + \alpha_k^*$, where $\beta_0 = \log(\theta)$ and $\alpha_k^* = \log \lambda_k^*$, then the maximum likelihood estimate of β_0 is the logarithm of the SMR given in (4). Thus, by fitting a Poisson regression model to d_{ik}, assuming the canonical log-link and including only an intercept parameter, β_0, and the logarithm of the expected number of deaths, $\log(y_{ik}\lambda_k^*)$, as an offset, provides an estimate for the standardized mortality ratio and its standard error.

4.2. *Extending the Standardized Mortality Ratio*

Generalization of the simple SMR to adjusted or stratum-specific SMRs can be obtained by appropriate stratification or inclusion of explanatory variables (including various time scale variables) in a Poisson multiplicative hazard structure. Breslow and Day (1987) and Clayton and Hills (1993) provided general discussions of such use of Poisson models for cohort studies.

To understand, however, how mortality risk in a patient cohort varies with calendar time, a futher extension of this methodology is useful. To achieve this, calendar time can be divided into overlapping periods of a fixed length and with a fixed overlap time for adjacent periods. These are used to define "rolling average" SMRs, that is SMRs for each period, that can be used to display the trends in SMRs over long periods of calendar time. Further adjustment of these, for the effects of time-constant explanatory variables measured at cohort entry, can be made through the inclusion of an additional offset into the Poisson models. This additional explanatory variable-adjustment offset is the same for all calendar periods and is the linear predictor obtained from a Poisson regression model that includes the relevant baseline explanatory variables and the logarithm of the expected deaths as an offset and is fit to the data from the entire follow-up period. The method is illustrated more fully by specific application in Sec. 4.4.

4.3. *Life Expectancy and Expected Age at Death*

It has been suggested that comparative measures such as the standardized mortality ratio are not as easily understood as alternative measures such as life expectancy

and years of life lost (Tsai et al., 1992). The standard definition of life expectancy of an individual who has reached a particular age is the average future number of years remaining for that individual if the current age-specific mortality rates do not change in the future. The years of life lost for a specific population would be the difference between the estimated life expectancies, calculated from the beginning of each patient's follow-up period, based on population mortality rates and on these rates multiplied by the SMR. This provides an indication of how the relative increase in mortality rates measured by the SMR translates to a more direct measure of its impact.

The mathematical representation of life expectancy (mean residual lifetime) of an individual known to have survived to an age x, e_x, in terms of the hazard function for age, $\lambda(u)$, is

$$e_x = \int_x^\infty \exp\left[-\int_x^t \lambda(u)du\right]dt,$$

with the expected age at death of the individual given survival up to age x, denoted by E_x, being

$$E_x = \int_x^\infty t\lambda(t)\exp\left[-\int_x^t \lambda(u)du\right]dt = x + e_x.$$

These two quantities can be estimated using life-table methods. As an illustration, consider the situation where the hazard function for age is piecewise constant over age-bands. That is,

$$\lambda(u) = \begin{cases} \lambda_0 & \sigma_0 \le u < \sigma_1 \\ \lambda_1 & \sigma_1 \le u < \sigma_2 \\ \vdots & \\ \lambda_{S-1} & \sigma_{S-1} \le u < \sigma_S \\ \lambda_S & \sigma_S \le u < \sigma_{S+1}, \end{cases}$$

where $\sigma_0 = 0$ and $\sigma_{S+1} = \infty$. If $x \in [\sigma_j, \sigma_{j+1})$ then it can be shown, after straightforward but tedious algebra, that

$$\begin{aligned} E_x = {} & (x - \sigma_{j+1}e^{-\lambda_j(\sigma_{j+1}-x)}) + \frac{1}{\lambda_j}(1 - e^{-\lambda_j(\sigma_{j+1}-x)}) \\ & + \sum_{k=j+1}^{S-1} e^{-\sum_{s=j}^{k-1}\lambda_s(\sigma_{s+1}-\sigma'_s)}\left[(\sigma_k - \sigma_{k+1}e^{-\lambda_k(\sigma_{k+1}-\sigma_k)}) + \frac{1}{\lambda_k}(1 - e^{-\lambda_k(\sigma_{k+1}-\sigma_k)})\right] \\ & + e^{-\sum_{s=j}^{S-1}\lambda_s(\sigma_{s+1}-\sigma'_s)}\left[\sigma_S + \frac{1}{\lambda_S}\right], \end{aligned} \tag{5}$$

where $\sigma'_s = x$, if $s = j$ and $\sigma'_s = \sigma_s$, if $s > j$. Furthermore, if we assume for the last age-band, $[\sigma_S, \sigma_{S+1})$, that $\lambda_S = \infty$, then the last term in (5) simplifies to $\sigma_S \exp[-\sum_{s=j}^{S-1}\lambda_s(\sigma_{s+1} - \sigma'_s)]$.

However, these equations are for the special case of piecewise constant hazards that vary only with age. In many applications in epidemiology and demography,

life table estimates of the age-specific mortality rates also vary with calendar time. Therefore, more general formulae for life expectancy and expected age at death, that allow hazards to vary with age and calendar time along the unit slope life-lines of individuals, are required. This can be done using the extended notation of Sec. 3.

The life expectancy of an individual age x at calendar time y can be written as

$$e_{xy} = \int_0^\infty \exp\left[-\int_0^u \lambda(x+v, y+v)dv\right]du,$$

and the expected age at death of that individual as

$$E_{xy} = \int_x^\infty u\lambda(u, y-x+u)\exp\left[-\int_x^u \lambda(v, y-x+v)dv\right]du = x + e_{xy},$$

when the age-specific mortality rates vary over calendar time.

Then, if we assume, as previously, that the hazard function for age and calendar time can be represented as piecewise constant in (age,time)-bins, say λ_{st} for an (age, time)-pair falling in the sth age-band and the tth calendar period, where $s = 0, \ldots, S$ and $t = 0, \ldots, T$, then the more general equations for life expectancy and age at death can be simplified in a similar manner to that of (5), with summations again replacing integrals, but now with the end-points (i.e., σ_j's) of age intervals for an individual being modified to additionally include the ages for which the endpoints of relevant calendar periods are projected onto the age-axis via that individual's life line equation. (Details are provided in the Appendix.)

The additional assumption, perhaps restricted to a particular subgroup, that the stratum-specific mortality rates are a constant multiplier θ of known stratum-specific reference mortality rates, as outlined earlier for the SMR (i.e., $\lambda_{st} = \lambda^*_{st}\theta$) then allows an SMR to be linked to life expectancies and to expected ages at death. From the appropriate formulae, the life expectancies and expected ages at death, at cohort entry, can be calculated for all individuals in the cohort (see (8)). The average of the expected ages at death will provide an estimate of the average projected death age of the cohort and can be calculated for the estimated SMR and for $\theta = 1$ for comparison. Similarly, average years of life lost for this cohort relative to a reference cohort can be calculated.

Note that if the baseline hazard for patients in the cohort are assumed unknown but the hazard is still assumed to be piecewise constant either over just the time-scale age (i.e., assuming $\log \lambda_i(s, t) = \mu + \alpha_s$), or over both age and calendar time (i.e., assuming either $\log \lambda_i(s, t) = \mu + \alpha_s + \pi_t + (\alpha\pi)_{st}$ or $\log \lambda_i(s, t) = \mu + \alpha_s + \pi_t$), then standard life table methods can be applied to obtain estimates of the hazard function and subsequently estimates of the life expectancies and expected ages at death for individuals in the cohort. However, depending on the size of the cohort and the number of deaths that have occurred in the cohort, these estimated parameters may be highly variable and thus the use of population rates may be more appealing.

4.4. *Application to the Toronto PSA Clinic*

For the Toronto PsA cohort, mortality data for the general population of Ontario, stratified by 5-year age-bands, sex, and calendar year (from 1978–2004) were used to calculate reference mortality rates (i.e., dynamic age-specific life tables for each

calendar year and for males and females separately). Overall, SMRs and male and female specific SMRs were calculated through the use of Poisson regression methodology.

We found that the overall SMR in the PsA patient cohort as compared to the general Ontario population, for the study period 1978–2004, was estimated to be 1.36 (95% CI: 1.12, 1.64). The gender-specific SMRs were 1.25 (95% CI: 0.95, 1.65) for men and 1.47 (95% CI: 1.13, 1.91) for women. Thus there is some indication of a slightly raised death rate amongst the PsA patients as opposed to the general Ontario population.

The overall SMR of 1.36 would correspond to the average years of life lost being estimated as 2.99 years (95% CI: 1.14, 4.77) in the Toronto PsA cohort.

To investigate time-trends in (excess) mortality rates for the PsA cohort, "rolling average" SMRs for 10-year overlapping calendar periods (1978–1987, 1979–1988, 1980–1989 to 1994–2003, and 1995–2004) were calculated. Again, Poisson regression models were used. Further, however, adjusted 10-year "rolling average" SMR analyses were performed with adjustment for patient characteristics at clinic entry. These characteristics, which might have influenced any unadjusted time trends in SMRs, included radiological damage, the interaction between sex and radiological damage, the logarithm of the sex-standardized erythrocyte sedimentation rate (a laboratory measure of acute inflammation), highest level of medication taken, presence or absence of hypertension, and disease activity (as measured by the number of joints with active disease). In addition we adjusted for smoking status at the time of PsA diagnosis. The Poisson model (2) was used to obtain the explanatory variable-adjustment offset, and there was no evidence that the mortality effects of these adjustment factors varied with calendar period. The results of the unadjusted and adjusted analyses are shown in Figs. 1 and 2.

In Fig. 1, a clear decline with calendar period is present in the complete cohort, as well as for men and women separately. Although initially, the SMRs for women

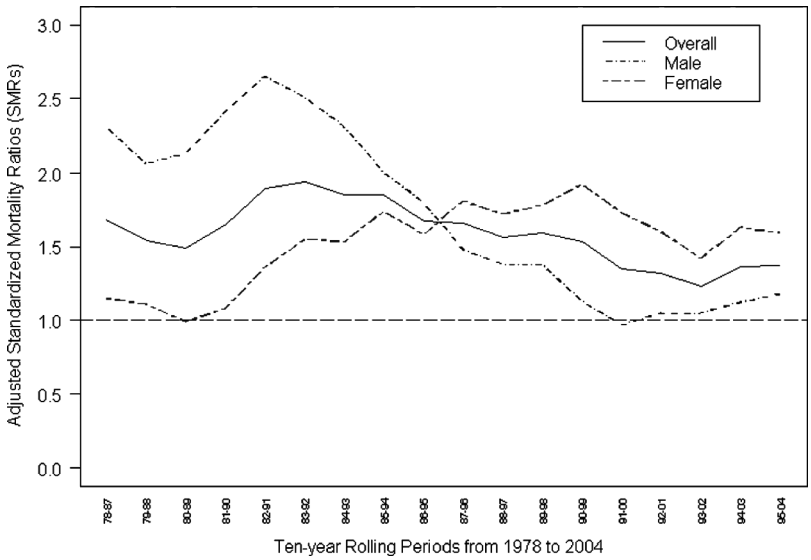

Figure 1. Unadjusted rolling SMR for PsA cohort.

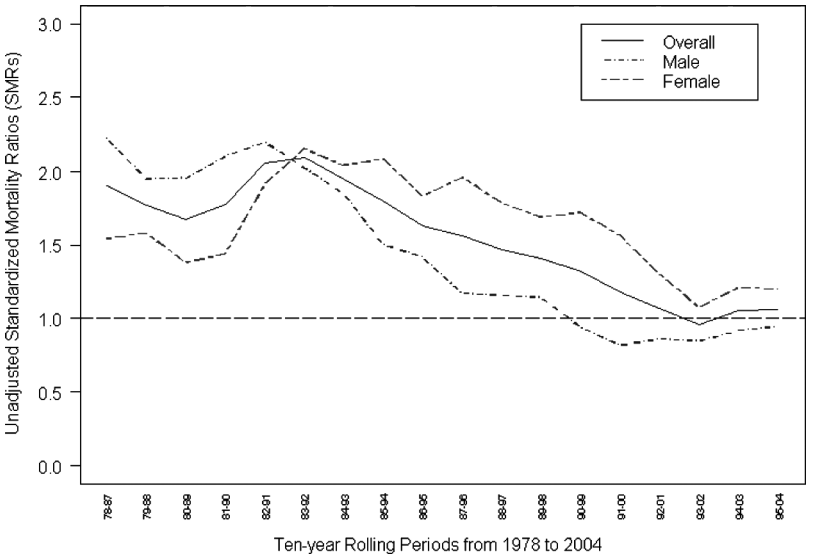

Figure 2. Adjusted rolling SMR for PsA cohort.

remained relatively constant at around 1.5 (indicating possible excess mortality), the values then increased and then gradually declined so in the latest time periods there was no indication of excess mortality for men or women.

Figure 2 presents the comparable curves adjusted for patient characteristics at entry. The level of the SMRs in this plot are not meaningful in themselves as they correspond only to patients with particular characteristics. More meaningful is the general pattern of these adjusted SMRs over the rolling 10-year periods. The adjustment for baseline characteristics at entry removes the effect of calendar time on the excess mortality for females. However, for males the dramatic decline seen in the unadjusted SMR curves remains. Therefore, for the entire cohort, a less marked decline is observed when adjustment is made for baseline characteristics of the patients.

5. Internal Comparisons

5.1. *Cox Regression Model*

The previous section outlined methods that assumed that the underlying baseline hazard, $\lambda_0(a, p)$ in (2) was known from an external source. These methods reflect traditional epidemiological approaches to the analysis of cohort studies. If the underlying baseline hazard function is unknown or functionally known up to certain unknown parameters, and cannot be approximated by mortality rates from a reference population, then the methodology in the previous section cannot be used. In addition, for many questions of interest, comparison with a standard population is not necessary and may therefore complicate an analysis. For example, analyses based only on cohort data can be used to investigate the prognostic effects of explanatory variables and to examine time trends.

For this purpose, the semi-parametric approach proposed by Cox (1972, 1975) for analysing time to event data is a natural choice and we illustrate it here. We do not discuss parametric approaches (e.g., Weibull models) to modelling this type of data. These may be a reasonable choice in some cases but lacks flexibility in the shape of the underlying hazards. The data we examine could also be analysed using age-period-cohort Poisson models following the general arguments of Sec. 4 but with estimation of the stratum specific hazards. Such models are often advocated when there is interest in time trends on multiple time scales but introduce non identifiability issues related to linear dependence among the age, calendar period and birth cohort time scales.

While Cox's model can be recommended solely on the basis of its generality, we should like to emphasize that, with individual patient data, the use of Cox's regression model is particularly useful in dealing with the multiple time scales that arise in the analysis of cohort data. Non identifiability issues may arise with this model but they are much less of an issue, if care is taken in the incorporation of time scales into the model, than for the traditional age-period-cohort models. Moreover, the greater identifiability means that there is the potential of identifying dominant time trends in the data. This will be demonstrated in Sec. 5.2 by example.

A stratified version of the model introduced by Cox (1972) specifies the hazard function, $\lambda(u)$, for an individual in the kth stratum, as a function of a baseline time scale u, as

$$\lambda_k(u; z) = \lambda_{0k}(u) \exp(\beta^T z(u)), \tag{6}$$

where the $\lambda_{0k}(u); k = 1, \ldots, K$ are unknown and unrelated underlying baseline hazard functions and $z(.)$ is a vector of explanatory variables, possibly time dependent. The effects, represented by the regression coefficient vector β, of the explanatory variables on survival are typically assumed to be the same regardless of the stratum but this can be examined. The stratification can be on a variety of explanatory variables for which proportional hazards assumptions may be inappropriate and which may not be of particular inferential interest. It can also depend on the various time scales suitably categorized.

In cohort mortality studies, with follow-up over a long period of time, age is typically chosen as the baseline time scale for the hazard function. While other scales, time on study (as in clinical trials) or calendar time, could be chosen, mortality rates would be expected to have a more complicated relationship to age than to either follow-up time or secular trends, and therefore age effects should be allowed to be as general as possible (Breslow et al., 1983). Other time scales may be introduced by stratification or as explanatory variables (see also Farewell and Cox, 1979). As alluded to above, the decision whether to introduce an explanatory variable for or to stratify on a time scale may partially depend on whether or not the variable is of direct interest. In the lupus example to be discussed in Sec. 5.2, time trends on various scales are of direct interest and therefore will be incorporated as explanatory variables to allow significance tests to be easily performed. With all other factors of interest also introduced as explanatory variables, the stratified Cox regression model may be replaced with the standard Cox regression model for the mortality hazard as a function of age u:

$$\lambda(u; z) = \lambda_0(u) \exp(\beta^T z(u)), \tag{7}$$

where, in particular, the explanatory variable vector $z(u)$ contains 'age-dependent' functions of the other time-scale variables (i.e., functions of the form $g(t(u))$, where $t \equiv t(u)$ is one of the other time scales).

Inference for models based on (6) or (7) proceeds in the standard way through use of Cox's (1975) partial likelihood,

$$L(\beta) = \prod_{k=1}^{K} \prod_{i(k)=1}^{n_k} \left[\frac{\exp(\beta^T z_{i(k)}(u_{i(k)}))}{\sum_{j(k)\in\mathcal{R}(u_{i(k)})} \exp(\beta^T z_{j(k)}(u_{i(k)}))} \right]^{d_{i(k)}}$$
$$= \prod_{k=1}^{K} \prod_{i=1}^{n_k} \left[\frac{\exp(\beta^T z_i(u_i))}{\sum_{j\in\mathcal{R}(u_i)} \exp(\beta^T z_j(u_i))} \right]^{d_i},$$

where $i(k)$ indicates the ith individual in the kth stratum, $u_{i(k)}$ is either age of death or age at censoring whichever occurred first, $d_{i(k)}$ is a censoring indicator, and the vector of explanatory variables is $z_{i(k)}(u_{i(k)})$. $\mathcal{R}(u_{i(k)})$ denotes the risk set of individuals who are alive and uncensored at a time just prior to $u_{i(k)}$ and in the kth stratum at that time. Simplification of the notation $i(k)$ to i and $j(k)$ to j is possible if it is clear that reference is to individuals observed in the kth stratum at particular ages.

Delayed entry or left truncation can be easily incorporated into the Cox regression model through the modification of the risk set to include only those individuals who have entered the cohort by and are thus observed to be at risk at a particular time.

5.2. *Application to the Toronto SLE Cohort*

Before illustrating the use of a time to event regression model with the Toronto SLE cohort, we present some results based on the more traditional methodology of Sec. 4 (Urowitz et al., 2008). The overall SMR and gender-specific SMRs for the Toronto Clinic over the period 1970–2005, relative to the mortality rates for the general population of Ontario, stratified by 5-year age-bands, sex, and calendar year, were, overall, 4.53 (95% CI: 3.96, 5.19); for males, 3.96 (95% CI: 2.90, 5.40); and, for females, 4.69 (95% CI: 4.04, 5.45). The estimate of overall years of life lost was 14.23 years (95% CI: 12.69, 15.76). There is thus, as is to be expected, a large excess mortality risk for patients in the Toronto Lupus cohort as compared to the general Ontario population and a dramatic reduction in the life span of this cohort.

Additionally, Table 1 presents SMRs tabulated by entry cohort and calendar period. Entry cohorts were defined by the period of entry into the cohort (1: 1970–1978, 2: 1979–1987, 3: 1988–1996, and 4: 1997–2005). The calendar effect was defined through the time periods (A: 1970–1978, B: 1979–1987, C: 1988–1996, and D: 1997–2005). Note that this table also contains within it a third time scale dimension corresponding to the time in the clinic and represented by the diagonals of the table.

It is clear from Table 1 that if SMRs were calculated for each column, corresponding to a calendar period, a decline over time would be evident. Equally though, it is evident that there are declines with increased disease duration, seen within rows, and with increased time in the clinic, seen across diagonals. These declines could contribute to the observed calendar period decline. Thus, based on such a table, there is some difficulty in linking particular trends in the SMRs to

Table 1
SMRs (in bold) by entry cohort and calendar period, with 95% confidence intervals (same row), and including number of patients (number of deaths) in each cell

Entry cohort	Follow-up (calendar) period			
	1970–1978	1979–1987	1988–1996	1997–2005
1970–1978	**13.84** (9.78, 19.56) 220 (32)	**4.86** (3.31, 7.13) 169 (26)	**3.07** (1.93, 4.87) 119 (18)	**3.23** (1.98, 5.28) 82 (16)
1979–1987		**6.45** (4.51, 9.22) 351 (30)	**3.54** (2.50, 5.01) 277 (32)	**3.92** (2.53, 6.08) 155 (20)
1988–1996			**4.24** (2.28, 7.88) 255 (10)	**3.93** (2.47, 6.23) 192 (18)
1997–2005				**3.81** (1.98, 7.32) 383 (9)

particular time scales. Essentially this arises because of the discretization of the various scales and the linear dependencies between scales.

To address this difficulty, we return to the individual patient-level data and fit a multivariate Cox regression model with age as the baseline time variable, and with calendar period, age at diagnosis (equivalent to the inclusion of disease duration) and entry cohort used to define explanatory variables in the parametric regression component of the model. Further, a natural question is whether any time trends that are observed are related to time trends in patients' entry characteristics or their disease course, the latter perhaps being linked to changing treatment strategies over time. For this purpose, other lupus-related variables and demographic variables (such as, sex, race, coronary artery disease (CAD), adjusted mean SLEDAI-2K (AMS) (Ibañez et al., 2003), and various medications) can also be included as explanatory variables.

While use of individual patient data avoids some of the indeterminacy of Table 1, the inclusion of four time scales in the model requires some avoidance of indeterminacy (non identifiability) by not formally examining time from entry, which is the difference between age and age at entry, in the model. However, this particular time scale is not of direct interest as it is difficult to imagine it biologically having an impact on mortality beyond that reflected by the other time variables in the analysis.

The results from fitting the Cox regression model are shown in Table 2 (Urowitz et al., 2008). As the effect of calendar period is highly significant ($p = 0.009$), while neither entry cohort ($p = 0.544$) nor age at diagnosis ($p = 0.508$) have demonstrable effects, this suggests that the most plausible explanation for the patterns seen in Table 1 is a calendar period effect on mortality rates, not linked to other measured variation in cohort patients or their management.

6. Conclusion

Poisson and Cox regression models provide highly flexible and useful ways to examine mortality, and other time to event outcomes, in prospective clinical cohorts of rheumatology patients. Poisson models are perhaps most useful when comparison with standard mortality rates is of primary interest while the advantages of Cox

Table 2
Multivariate Cox regression model

	Variable	Hazard ratio	Lower 95% CI	Upper 95% CI	*p*-value
Sex:	Male v Female	1.76	1.15	2.69	0.009
Race					0.059
	Black v Caucasian	1.52	0.87	2.69	
	Chinese v Caucasian	1.96	0.97	3.94	
	Other v Caucasian	1.95	0.92	4.15	
Age at diagnosis		1.01	0.98	1.03	0.508
Entry cohort					0.544
	1979–1987 v 1970–1978	1.3	0.83	2.03	
	1988–1996 v 1970–1978	0.99	0.5	1.96	
	1997–2005 v 1970–1978	0.97	0.34	2.76	
Calendar period					0.009
	1979–1987 v 1970–1978	0.77	0.44	1.34	
	1988–1996 v 1970–1978	0.43	0.22	0.82	
	1997–2005 v 1970–1978	0.27	0.12	0.61	
CAD event ever:	Yes v No	1.52	1.02	2.26	0.041
AMS		1.15	1.11	1.2	<0.0001
SDI		1.24	1.14	1.35	<0.0001
Immunosuppressives ever used:	Yes v No	1.71	1.17	2.51	0.006
Steroids at assessment:	Yes v No	1.12	0.72	1.75	0.624
Antimalarials at assessment:	Yes v No	0.58	0.39	0.87	0.009

models are most evident with analyses that involve comparisons of patients within a cohort. Their application requires, however, that careful consideration be given to the model specification.

The use of Poisson models with the psoriatic arthritis cohort data demonstrated that a single SMR might be an appropriate summary measure for female patients over the 26 years of follow-up, but only if it is adjusted for variation in patient characteristics at clinic entry. For males, a single SMR would not be appropriate since there is a downward trend in the SMR over calendar time which is present in both adjusted and unadjusted analyses. In the analysis of the lupus cohort data, relative risk regression models allowed the identification of a calendar period effect not confounded with entry cohort, age at diagnosis, or changes in patient characteristics at entry to the lupus clinic.

Other methods may also be useful and sometimes represent special cases of, or approximations to, the regression methodology discussed here. Nevertheless, when individual patient data are available, this methodology provides many advantages. Simpler and more traditional methods are included as special cases and are thus easily generalized. This represents an important gain with the only drawbacks being the use of more sophisticated statistical packages and the greater challenge of explaining the methods to medical researchers with various levels of statistical understanding. As for other methods in the past, their greater use will help alleviate the latter challenge while enhancing the value of rheumatological cohort data.

Appendix

Expected Age of Death Calculation for Two Time-Scales

Consider an individual who reaches a particular age $x \in [\sigma_j, \sigma_{j+1})$ at calendar date/time $y \in [\tau_k, \tau_{k+1})$, where $[\sigma_j, \sigma_{j+1})$ and $[\tau_k, \tau_{k+1})$ denote the jth age-band and the kth calendar period respectively. This individual from age x onwards will potentially go through a sequence of age-bands $\{[\sigma_j, \sigma_{j+1}), [\sigma_{j+1}, \sigma_{j+2}), \ldots, [\sigma_S, \sigma_{S+1})\}$ over his/her life time. Furthermore, within each of these age-bands (above), the individual will potentially traverse an associated finite (nested) subsequence of calendar periods. That is, the individual whilst in an age-band $[\sigma_s, \sigma_{s+1}) \in \{[\sigma_j, \sigma_{j+1}), [\sigma_{j+1}, \sigma_{j+2}), \ldots, [\sigma_S, \sigma_{S+1})\}$, will potentially enter a finite subsequence of calendar periods $\{[\tau_{v_s}, \tau_{v_s+1}), [\tau_{v_s+1}, \tau_{v_s+2}), \ldots, [\tau_{v_s+k_s}, \tau_{v_s+k_s+1})\}$ before exiting this age-band, where v_s indexes the first calendar period the individual entered into after entering the sth age-band after age x and calendar date y.

Now define

$$\Delta_{xy}(s, v_s + n) = \min(\sigma_{s+1}, u(v_s + n)) - \max(x, \sigma_s, l(v_s + n)), \quad \text{for } n = 0, \ldots, k_s,$$

where $u(v_s + n)$ is the age of the individual when exiting the calendar period $[\tau_{v_s+n}, \tau_{v_s+n+1})$ and $l(v_s + n)$ is the age of the individual when entering the calendar period $[\tau_{v_s+n}, \tau_{v_s+n+1})$. Then for this individual age x at calendar time y, the expected age at death is given by

$$\begin{aligned} E_{xy} &= \int_x^\infty u\lambda(u, y - x + u) \exp\left[- \int_x^u \lambda(v, y - x + v) dv \right] du \\ &= \sum_{s=j}^{S} \sum_{n=0}^{k_s} \exp\left[- \sum_{r=j}^{s} \sum_{m=0}^{n-1} \lambda_{r, v_r+m} \Delta_{xy}(r, v_r + m) \right] \\ &\quad \times \left\{ - (\max(x, \sigma_s, l(v_s + n)) - \min(\sigma_{s+1}, u(v_s + n)) e^{-\lambda_{s, v_s+n} \Delta_{xy}(s, v_s+n)}) \right. \\ &\quad \left. + \frac{1}{\lambda_{s, v_s+n}} (1 - e^{-\lambda_{s, v_s+n} \Delta_{xy}(s, v_s+n)}) \right\}, \end{aligned} \tag{8}$$

which can be seen to be a generalization of (5) that takes account of the variation in mortality rates over the two time-scales, age and calendar time.

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References

Aitkin, M., Clayton, D. (1980). The fitting of exponential, Weibull and extreme value distributions to complex censored survival data using GLIM. *Appl. Statist.* 29:156–163.

Ali, Y., Tom, B. D. M., Schentag, C. T., Farewell, V. T., Gladman, D. D. (2007). Improved survival in psoriatic arthritis with calendar time. *Arthritis Rheum.* 56:2708–2714.

Berry, G. (1983). The analysis of mortality by the subject-years method. *Biometrics* 39:173–184.

Breslow, N. E., Day, N. E. (1987). *Statistical Methods in Cancer Research, Vol. II: The Design and Analysis of Cohort Studies*. IARC Scientific Publications 82. Lyon: International Agency for Research on Cancer.

Breslow, N. E., Lubin, J. H., Marek, P., Langholz, B. (1983). Multiplicative models and cohort analysis. *J. Amer. Statist. Assoc.* 78:1–12.

Clayton, D., Hills, M. (1993). *Statistical Models in Epidemiology*. Oxford: Oxford University Press.

Cox, D. R. (1972). Regression models and life tables (with discussion). *J. Roy. Statist. Soc. Ser. B* 34:187–220.

Cox, D. R. (1975). Partial likelihood. *Biometrika* 62:269–276.

Dickman, P. W., Sloggett, A., Hills, M., Hakulinen, T. (2004). Regression models for relative survival. *Statist. Med.* 23:51–64.

Farewell, V. T., Cox, D. R. (1979). A note on multiple time scales in life testing. *Appl. Statist.* 28:73–75.

Frome, E. (1983). The analysis of rates using Poisson regression models. *Biometrics* 39:665–675.

Gladman, D. D. (2004). Psoriatic arthritis. In: Harris, E. D., Budd, R. C., Firestein, G. S., Genovese, M. C., Sergent, J. S., Ruddy, S., Sledge, C. B., eds. *Kelly's Textbook of Rheumatology*. 7th ed. Philadelphia: W.B. Saunders Co., pp. 1155–1164.

Holford, T. R. (1980). The analysis of rates and survivorship using log-linear models. *Biometrics* 36:299–305.

Holford, T. R. (2005). Age–period–cohort analysis. In: Armitage, P., Colton, T., eds. *Encyclopedia of Biostatistics, Volume 1*. Chichester: John Wiley & Sons, Inc., pp. 82–99.

Ibañez, D., Urowitz, M. B., Gladman, D. D. (2003). Summarizing disease features over time: I. adjusted mean SLEDAI derivation and application to an index of disease activity in lupus. *J. Rheumatol.* 30:1977–1982.

Laird, N., Olivier, D. (1981). Covariance analysis of censored survival data using log-linear analysis techniques. *J. Amer. Statist. Assoc.* 76:231–240.

Tsai, S. P., Hardy, R. J., Wen, C. P. (1992). The standardized mortality ratio and life expectancy. *Amer. J. Epidemiol.* 135:824–831.

Urowitz, M. B., Gladman, D. D. (2000). How to improve morbidity and mortality in systemic lupus erythematosus. *Radiology* 39:238–244.

Urowitz, M. B., Gladman, D. D., Tom, B. D., Ibañez, D., Farewell, V. T. (2008). Changing patterns in mortality and disease outcomes for systemic lupus erythematosus (SLE) patients. *J. Rheumatol.* 35:2152–2158.

Whitehead, J. (1980). Fitting Cox's regression model to survival data using GLIM. *Appl. Statist.* 29:268–275.

Whittemore, A. S. (1985). Analyzing cohort mortality data. *Amer. Statistician* 39:437–441.